

**INFLUENCE OF CROSPVIDONE ON THE ORAL BIOAVAILABILITY OF A
MODEL DRUG AND TOXIN**

by

TAN SIEW SIEW

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To my beloved parents and family members

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PENGARUH CROSPVIDONE KE ATAS BIOKEPEROLEHAN ORAL DRUG DAN TOKSIN MODEL

ABSTRAK

Kajian ini dijalankan untuk menyiasat potensi crospovidone dalam pencegahan toksisiti aflatoxin B₁ serta kebolehannya untuk meningkatkan biokeperolehan oral drug yang mempunyai keterlarutan rendah dalam air, iaitu ibuprofen. Pada peringkat awal kajian ini, satu kaedah kromatografi cecair prestasi tinggi yang ringkas, spesifik dan sensitive telah berjaya dibangunkan untuk menentukan kepekatan aflatoxin B₁ dalam plasma. Kaedah ini mempunyai kejituan dan ketepatan yang baik bagi julat kepekatan dari 0.1 ng/ml ke 50.0 ng/ml.

Pelbagai faktor yang mempengaruhi penyerapan aflatoxin B₁ terhadap crospovidone, seperti kepekatan crospovidone, masa hidrasi, masa reaksi, pH and nisbah drug kepada polimer telah dikaji untuk mendapatkan keadaan optimum bagi penyediaan formulasi aflatoxin B₁-crospovidone. Seterusnya, satu formulasi aflatoxin B₁-crospovidone dengan nisbah drug kepada polimer 1:200 yang disediakan dalam keadaan optimum telah diberikan kepada tikus Sprague-Dawley dalam satu kajian *in vivo*. Kajian biokeperolehan ini telah dijalankan mengikut rekabentuk perbandingan selari untuk menyelidik biokeperolehan oral aflatoxin B₁ dalam bentuk larutan akueus aflatoxin B₁ dan formulasi aflatoxin B₁-crospovidone. Walau bagaimanapun, profil plasma bagi kedua-dua formulasi didapati tidak menunjukkan perbezaan yang ketara. Ini menunjukkan bahawa crospovidone tidak mengubah biokeperolehan aflatoxin B₁ dengan signifikan.

Selain itu, kebolehan crospovidone untuk meningkatkan biokeperolehan oral ibuprofen juga telah dijalankan dengan menggunakan tikus. Kajian *in vivo* ini telah dijalankan

mengikut rekabentuk bersilang dua-hala untuk membanding biokeperolehan oral bagi formulasi ibuprofen-crospovidone dalam larutan penimbal fosfat pH 2.4 dengan suspensi ibuprofen dalam larutan penimbal fosfat pH 2.4. Kajian tersebut menunjukkan bahawa formulasi ibuprofen-crospovidone dapat meningkatkan biokeperolehan oral ibuprofen sebanyak kira-kira 5 kali berbanding dengan suspensi ibuprofen. Kesimpulannya, crospovidone didapati dapat membantu meningkatkan biokeperolehan oral drug yang mempunyai keterlarutan rendah dalam air seperti ibuprofen.

INFLUENCE OF CROSPVIDONE ON THE ORAL BIOAVAILABILITY OF A MODEL DRUG AND TOXIN

ABSTRACT

The present study was conducted to evaluate the potential of crospovidone in preventing aflatoxin B₁ toxicity as well as its ability to enhance the oral bioavailability of a poorly water-soluble drug, namely ibuprofen. In the first part of the study, a simple, specific and sensitive high performance liquid chromatographic method was successfully developed for the analysis of aflatoxin B₁ in plasma. The method has good precision and accuracy over concentrations ranging from 0.1 ng/ml to 50.0 ng/ml.

Various factors affecting the adsorption of aflatoxin B₁ to crospovidone, such as concentration of crospovidone, hydration time, contact time, pH and drug to polymer ratio were investigated to obtain the optimum conditions for preparation of aflatoxin B₁-crospovidone formulation. Subsequently, an aflatoxin B₁-crospovidone formulation with a drug to polymer ratio of 1:200 was administered to Sprague-Dawley rats in an *in vivo* study. This comparative bioavailability study was conducted according to a parallel study design to evaluate the oral bioavailability of aflatoxin B₁ administered as an aqueous solution and aflatoxin B₁-crospovidone formulation. The plasma profiles of the two preparations were closely similar indicating that crospovidone did not significantly alter the oral bioavailability of aflatoxin B₁.

The ability of crospovidone for enhancing oral bioavailability of ibuprofen was also evaluated in rats. The *in vivo* evaluation was conducted according to a crossover study design to compare the oral bioavailability of ibuprofen-crospovidone formulation in phosphate buffer pH 2.4 and ibuprofen suspension in phosphate buffer pH 2.4. The study showed that the ibuprofen-crospovidone formulation could increase the oral

availability of ibuprofen by approximately 5.0 times compared to the ibuprofen suspension. In conclusion, crospovidone was found to be useful in enhancing the oral bioavailability of a poorly water-soluble drug such as ibuprofen.

CHAPTER 1

INTRODUCTION

1.1 Bioavailability and absorption of drugs

1.1.1 Introduction

The terms oral absorption and oral bioavailability are widely used in the pharmacokinetic and biopharmaceutic literature. They have been treated either identically or differently in several widely cited books and created confusion in publications (Chiou, 2001). Oral absorption is defined as the process by which a drug proceeds from the site of administration (mouth) to the site of measurement (systemic circulation) within the body (Rowland and Tozer, 1980) whereas oral bioavailability refers to the rate and extent of absorption of a drug from its dosage form into the systemic circulation (Wagner, 1975).

1.1.2 Oral drug absorption

There are many routes of drug administration such as oral, intravenous, transdermal, intramuscular, subcutaneous, buccal, nasal, rectal and inhalation. Of these, the oral route remains the most preferred because it is the simplest, most convenient and safest means of drug administration (York, 2002). However, there are some disadvantages associated with oral dosing. One of the disadvantages is the interindividual and intraindividual variations in both the rate and extent of oral absorption (Lin et al., 1999). Other disadvantages, include poor stability of some drugs in the low pH of the gastric juices, first-pass metabolism effect of the liver and difficulty in swallowing the dosage form (Barich et al., 2005).

Gastrointestinal tract is a muscular tube of approximately 6 m in length stretching from the mouth to the anus. The four main anatomical areas are the oesophagus, stomach, small intestine and large intestine. The mouth is the point of entry for oral drugs. It is

linked to the stomach via the oesophagus (Ashford, 2002a). In the stomach, the ingested solids are reduced to chyme by the action of acid and enzymatic digestion (Washington et al., 2001a).

The next part of the gastrointestinal tract to be encountered by pharmaceuticals is the small intestine, which enables efficient absorption of nutrients, fluids, electrolytes, and drugs, as well as the simultaneous exclusion of antigenic or toxic inflammatory substances (Knutson et al., 2000). The large intestine is the final part of the gastrointestinal tract. It is concerned primarily with the absorption of water and secretion of mucus to aid the unabsorbed intestinal contents to slide down the intestines (Florence and Attwood, 1988a).

For a drug molecule to be orally bioavailable, it has to traverse the epithelial layer of the gastrointestinal tract. It needs to remain in solution in order to be absorbed. The drug then needs to diffuse across the mucous layer, across the unstirred water layer, and subsequently across the gastrointestinal membrane. After passing through this cellular barrier the drug encounters the liver before it reaches the systemic circulation (Ashford, 2002a). Moreover, the drug must overcome the chemical barrier which consists of metabolizing enzymes that can degrade it. At the same time, it must have optimal physiochemical properties for its permeation across the biological barriers (Calcagno and Siahaan, 2005).

Thus, there are many factors that can influence the rate and extent of drug absorption and these include physiological, physicochemical and formulation factors and they are briefly discussed in the following sections.

1.1.3 Physiological factors influencing oral drug absorption

1.1.3(a) Membrane permeability

The gastrointestinal membrane separates the lumen of the stomach and intestines from the systemic circulation. It is the main barrier to the absorption of drugs from the gastrointestinal tract. The membrane is semipermeable in nature. It allows the passage of lipid-soluble molecules across it and the passage of water and small hydrophilic molecules through its numerous aqueous pores. Additionally, there are some transporter proteins that exist in the membrane which transport materials back and forth across it (Ashford, 2002a).

As most drugs are weak electrolytes, it is expected that the unionised form of either acidic or basic drugs, being the lipid soluble species, will diffuse across the gastrointestinal membrane while the ionised forms will be rejected. This is the basis of the pH-partition hypothesis in which drug absorption and solute transport across membrane is pH dependent (Florence and Attwood, 1988a). However, absorption is a dynamic process involving dissolution, ionization, partition and blood flow, and consequently the correlation of pH-partition predictions with experiments is often poor (Washington et al., 2001b).

1.1.3(b) Membrane transport mechanism

There are two main mechanisms of drug transport across the gastrointestinal membrane, the transcellular and paracellular. The transcellular or across the cell pathway is further divided into simple passive diffusion, carrier-mediated transport and endocytosis.

Passive diffusion is the major route of transport for relatively small lipophilic molecules encompassing many drugs. Passive diffusion is a term used to characterize the movement of drug molecules down a concentration gradient without cellular

penditure of energy. This process is neither saturable nor inhibited by other molecules (Bourne et al., 1986). The rate of transport is determined by the physicochemical properties of the drug, the nature of the membrane and the concentration gradient of the drug across the membrane (Ashford, 2002a). The drug transport rate of passive diffusion increases in parallel with drug lipophilicity and inversely with the square root of molecular size (Terasaki and Ohtsuki, 2005).

There are certain compounds that are absorbed transcellularly by a carrier-mediated transport mechanism, of which there are two main types, active transport and facilitated diffusion. In active transport, materials can be transported across membrane against a concentration gradient. This process requires metabolic energy and it can be inhibited by inhibitors of cellular energy metabolism (Bourne et al., 1986).

There are a large number of carrier-mediated active transport systems in the small intestine such as the peptide transporters, nucleoside transporters, sugar transporters, bile acid transporters, organic anion transporters and vitamin transporters. Many nutrients, such as amino acids, sugars, electrolytes, vitamins and bile salts are actively transported (Ashford, 2002a). The peptide-like drugs, such as the β -lactam antibiotics, angiotensin-converting enzyme inhibitors, and bestatin, rely on the intestinal dipeptide transporter PepT1 for their efficient absorption (Lee, 2000).

On the other hand, facilitated diffusion differs from active transport in that it cannot transport a substance against a concentration gradient of that substance. Therefore, facilitated diffusion does not require an energy input but does require a concentration gradient for its driving force (Ashford, 2002a). Another type of transcellular transport is by endocytosis. Endocytosis is the uptake of extracellular material, exogenous molecules, or macromolecules into a cell by invagination of the plasma membrane and vesicle formation (Ritschel and Kearns, 2004a).

The paracellular pathway is the transport of materials in the aqueous pores between the cells rather than across them. The cells are joined together via closely fitting tight junctions on their apical side. The paracellular route of absorption is important for the transport of ions such as calcium and for the transport of sugars, amino acids and peptides at concentrations above the capacity of their carriers. Small hydrophilic and charged drugs also cross the gastrointestinal epithelium via the paracellular pathway. The molecular weight cut-off for the paracellular route is usually considered to be 200 Da (Ashford, 2002a).

1.1.3(c) Gastrointestinal pH

The pH of fluids along the gastrointestinal tract varies considerably. The gastric juice is highly acidic, with a pH within the range of 1 – 3.5 in the fasted state. However, the intestinal pH values are higher than gastric pH values with pH ranges between 4.4 – 7.4 (Ashford, 2002a). Many drugs are ionisable within the physiological pH range (Ozturk et al., 1988), which impacts their aqueous solubility (TenHoor et al., 1991). For drugs absorbed by passive diffusion, those exhibiting low aqueous solubility tend to have a slower oral absorption rate than those exhibiting high aqueous solubility (Kwan et al., 1986).

The pH of the gastrointestinal tract may also affect the rate of dissolution of a drug from a formulation, or drug stability. The effect of pH on drug stability can be exemplified by the acid-labile penicillin antibiotics and certain polypeptides such as insulin (Bourne et al., 1986). The result of this instability is incomplete and poor bioavailability, as only a fraction of the administered dose reaches the systemic circulation in the form of intact drug (Ashford, 2002a).

1.1.3(d) Gastric emptying rate

Stomach acts as a reservoir, and regulates the passage of materials to the duodenum and small intestine where absorption takes place. As the absorptive capacity of the small intestine is far larger than that of the stomach, the gastric emptying rate may profoundly influence the rate and extent of absorption (Bourne et al., 1986, Ritschel and Kearns, 2004b). Gastric emptying of pharmaceuticals is highly variable and is dependent on the dosage form and the fed or fasted state of the stomach. Normal gastric residence time usually ranges between 5 minutes and 2 hours (Ashford, 2002a).

A number of factors can influence the gastric emptying rate. These include the amount and composition of food (Palin et al., 1982), viscosity of gastrointestinal content (Smart and Kellaway, 1989) and drug given concomitantly (Levy et al., 1972). Other physiological factors such as position of body and exercise were reported to have a limited effect. However, penicillins are unstable in acid and decompose if stomach emptying is delayed. Other drugs, such as aspirin, may irritate the gastric mucosa during prolonged contact (Shargel and Yu, 1993).

1.1.3(e) Intestinal transit and motility

The intestinal transit time is an important factor in determining efficient drug absorption because it determines the residence time of the drug in the absorption site (Kimura and Higaki, 2002). Mean small intestinal transit time has been found consistent, between 3 and 4 hours, and is independent of fed or fasted state conditions (Yu et al., 1996). However, some drugs (Greiff and Rowbothan, 1994) and drug excipients (Basit et al., 2002) have been shown to influence the extent of drug absorption by accelerating the intestinal transit.

On the contrary, the colonic transit of pharmaceuticals is long and variable. It can vary from anything between 2 and 48 hours (Ashford, 2002a). The human colon has a lower

absorption capacity than the small intestine, but its contents remain in the human colon for much longer. The long colonic residence time provides a significant opportunity for the slow absorption of drugs that are either targeted specifically or those remaining unabsorbed after reaching the colon (Edwards, 1997).

1.1.3(f) Perfusion of the gastrointestinal tract

The blood flow to the gastrointestinal tract is important in carrying the absorbed drug to the systemic circulation. A large network of capillaries and lymphatic vessels perfuse the small intestine. The splanchnic circulation receives about 28% of the cardiac output (Shargel and Yu, 1993). Blood flow to the gastrointestinal tract and liver increases shortly after a meal, thereby increases hepatic drug delivery and reduces presystemic metabolism (Ashford, 2002a). Thus, for drugs exhibiting a large first-pass effect such as propranolol, concomitant intake with food may increase drug bioavailability due to reduced presystemic metabolism (Liedholm et al., 1990). Besides, gastrointestinal blood supply may be reduced in certain disease states such as congestive heart failure (Carlton et al., 1996).

The majority of orally administered drugs gain access to the systemic circulation by absorption into the portal blood. However, some lipophilic compounds are transported via the intestinal lymphatics to the systemic circulation (Porter and Charman, 1997). The lymphatics are important in the absorption of dietary lipids, fat soluble vitamins (A, D, E and K) and many lipophilic drugs such as cyclosporine (Ueda et al., 1983). Absorption of drugs through the lymphatic system bypasses the first-pass effect due to liver metabolism (Shargel and Yu, 1993).

1.1.3(g) Food-drug interaction

The presence of food in the gastrointestinal tract can influence the rate and extent of absorption of the drug. Food can influence drug absorption through physicochemical

physiological interactions (Fleisher et al., 1999). One of the effects is the complexation of drugs with components in the diet, forming insoluble complexes. The portion of the administered dose that becomes complexed is unavailable for absorption (Ashford, 2002a). One example is tetracycline which forms non-absorbable complexes with calcium (Kakemi et al., 1968).

The presence of food also influences drug absorption by altering the intestinal pH and solubility of drugs, delaying gastric emptying, stimulating gastrointestinal secretions, creating competition for specialized absorption mechanisms and increasing the viscosity of gastrointestinal contents (Ashford, 2002a). Food-drug interactions may cause reduced, delayed, increased or accelerated absorption (Fleisher et al., 1999).

1.3(h) First-pass metabolism

The metabolism of drugs before entering the systemic circulation is referred to as first-pass metabolism (Lin et al., 1999). Metabolism of drugs administered orally may occur either in the gut wall or in the liver (Washington et al., 2001c). All drugs that are absorbed from the stomach, small intestine and upper colon pass into the hepatic portal system and are presented to the liver before reaching the systemic circulation. Hence, an oral dose of drug could be completely absorbed but incompletely available to the systemic circulation due to first-pass metabolism by enzymes in the gut wall or liver (Ashford, 2002a).

The cytochrome P450 (CYP) enzymes are a large family of enzymes expressed predominantly in the liver, but are found in many other tissues, and play a role in the metabolic clearance of many drugs (Humphreys, 2005). Among them, CYP3A4 is the most important enzyme because it is found in the greatest quantity and it has the broadest range of known substrate. For example, cyclosporine A is susceptible to

extensive gut and liver metabolism by CYP3A4, resulting in a significant reduction in its bioavailability (Wu et al., 1995).

1.1.3(i) The intestinal drug efflux

There are countertransport efflux proteins in the plasma membrane that actively remove a wide range of structurally and functionally distinct molecules back into the lumen of the gastrointestinal tract after they have been absorbed (Zhang and Morris, 2005). One of these proteins is P-glycoprotein. P-glycoprotein is a transmembrane efflux protein found in tumour cells. Besides, it is detected in the adrenal glands and on the apical side of the epithelial cells in the liver, kidney, pancreas and intestine (Thiebaut et al., 1987).

Since P-glycoprotein is expressed in high levels on the apical surface of columnar cells in the jejunum, it may affect the absorption and bioavailability of drugs (Ashford, 2002a). There are a number of drugs with wide structural diversity such as cyclosporine A, vinca alkaloids, digoxin, erythromycin, antibiotics and cimetidine that are susceptible to efflux from the intestine via P-glycoprotein (Washington et al., 2001c). Such efflux may have a detrimental effect on drug bioavailability.

1.1.4 Physicochemical factors

1.1.4(a) Lipophilicity

Biological membranes are lipoidal in nature and are more permeable to lipid soluble substances. Therefore, transport across these membranes depends, in part, on the lipid solubility of the diffusing species (Kwan et al., 1986). The octanol/water partition coefficients ($\log P$) is widely used as an indication of the lipid solubility of a drug, and whether that drug is liable to be transported across membranes (Ashford, 2002b).

Drug absorption usually increases as the lipophilicity rises. This has been shown with a series of β -blockers (Taylor et al., 1985). However, the rate of passive diffusion across the biological membrane will increase exponentially with increasing lipophilicity and then level off at higher lipophilicity due to a decrease in water solubility (Hu, 2005).

1.1.4(b) Stability

Chemical stability of a drug in the gastrointestinal fluids is very important. If the drug is unstable in the gastrointestinal fluids, the amount of drug that is available for absorption will be reduced and its bioavailability also reduced. Besides, chemical degradation products may adversely affect the physicochemical properties of a formulated product and may even be toxic (Barich et al., 2005). Chemical instability is often a function of pH. Therefore, stability in acid is a concern particularly for drugs intended for oral administration (Kwan et al., 1986). The antibiotic, erythromycin (Cachet et al., 1989) and proton pump inhibitor, omeprazole (Türkoğlu et al., 2004) degrade rapidly at acidic pH values and therefore are formulated as enteric-coated dosage forms to ensure good bioavailability (Ashford, 2002a).

1.1.4(c) Solubility

Drug absorption requires that molecules be in solution at the absorption site and dissolution depends in part on the solubility of the drug substance in the surrounding medium (Kwan et al., 1986). Therefore, the lack in the ability of a drug to go into solution is sometimes a more important limitation to its overall rate of absorption than its ability to permeate the intestinal mucosa (Hörter and Dressman, 2001). Solubility of drugs that are weak electrolytes is affected by pH due to the effects of pH on drug ionisation. Generally, ionised drugs tend to exhibit far greater aqueous solubility than the unionised counterpart (Martinez and Amidon, 2002).

The solubility of weakly acidic drugs increases with pH while the solubility of weak bases decreases with increasing pH. Hence, the solubility of a drug may change when it moves down the gastrointestinal tract from the stomach to the intestine (Ashford, 2002b). For instance, the antifungal drug ketoconazole, a weak base, is particularly sensitive to gastric pH. It has been reported that an increase in gastric pH produced by cimetidine or antacids decreases the absorption of ketoconazole (Männistö et al., 1982).

1.1.4(d) Particle size

Particle size is another parameter that influences drug dissolution, and in turn, drug absorption. Small particles with greater surface area dissolve more rapidly than larger particles, even though both have the same intrinsic solubility (Kwan et al., 1986). Therefore, particle size reduction is likely to result in increased bioavailability, provided the absorption of the drug is dissolution-rate limited (Ashford, 2002b). For example, the absorption of a poorly water soluble drug, griseofulvin, was doubled when the particle size was decreased from about 10 μm to 2.7 μm (Atkinson et al., 1962, Chattopadhyay and Gupta, 2001).

1.1.4(e) Dissociation constant

The dissociation constant (pK_a) of a drug and the pH at the absorption site often influence the absorption characteristics of a drug throughout the gastrointestinal tract (Ashford, 2002b). According to the pH-partition hypothesis of drug absorption, the unionised species of acidic or basic compounds in solution penetrates lipoidal membranes of the gastrointestinal tract more efficiently than the ionised species. Therefore, the rate of absorption of a drug is directly related to the concentration of its unionised species at the absorption site (Kwan et al., 1986). This means that a weakly acidic drug is more likely to be absorbed from the stomach where it is unionised, and a weakly basic drug from the intestine where it is predominantly unionised.

However, there are limitations of this hypothesis. This hypothesis is valid only if factors such as surface area and pH of stomach and small intestine are constant. In fact, the significantly larger surface area in the small intestine and a longer small intestinal residence time are thought to aid the absorption of drug regardless of their degree of ionisation (Ashford, 2002b).

1.1.4(f) Crystal form

Polymorphs are crystal forms caused by differences in the packing and orientation of molecules under different crystallizing conditions. The physicochemical properties of these crystal forms such as density, solubility and melting point are influenced by the intermolecular forces present (Kwan et al., 1986). A metastable polymorph usually has a higher solubility and exhibits a greater dissolution rate than the corresponding stable polymorph. Consequently, the metastable polymorphic form of a poorly soluble drug may exhibit an increased bioavailability compared to the stable polymorphic form (Ashford, 2002b).

However, the metastable polymorphs have the potential to convert to a more thermodynamically stable form leading to reduced solubility for the formulated product (Barich et al., 2005). One example is ritonavir, a protease inhibitor compound used to treat acquired immune deficiency syndrome (AIDS). This compound began production in a semisolid form and an oral liquid form. The appearance of a thermodynamically more stable polymorph with lower solubility led to a temporary withdrawal of the solid form from the market (Bauer et al., 2001).

1.1.5 Dosage form factors

1.1.5(a) Type of dosage form

The type of dosage form and its method of preparation can influence the bioavailability. In general, the type of oral dosage form will influence the release of drug into solution

and hence the appearance of dissolved drug in the gastrointestinal tract. The bioavailability of a drug tends to be higher for liquid dosage forms like aqueous solutions and aqueous suspensions and lower for solid dosage forms such as capsules and tablets (Ashford, 2002b).

1.1.5(b) Influence of excipients

Most drugs intended for oral administration require formulation with excipients to allow for adequate absorption, to facilitate manufacturing of the product, to increase the stability of the formulation, for aesthetic reasons or for identification (Jackson et al., 2000). Excipients have been classified according to the functions they perform in a formulation. These include disintegrating agents, diluents, lubricants, suspending agents, emulsifying agents, flavouring agents, colouring agents and chemical stabilizers (Ashford, 2002b).

Excipients have traditionally been thought of as being inert, but experience has shown that they can interact with a drug to affect its absorption and bioavailability (Jackson et al., 2000). For instance, the potential influence of excipients on drug bioavailability has been shown by formation of poorly soluble, non-absorbable drug-excipient complexes between tetracyclines and dicalcium phosphate, amphetamine and sodium carboxymethylcellulose, and phenobarbitone and polyethylene glycol (PEG) 4000 (Ashford, 2002b).

1.1.6 Methods to improve oral bioavailability

Increasing the bioavailability of drugs administered orally remains a challenge in drug development. Many techniques including chemical modifications and formulation approaches have been employed to overcome the problems of poor and erratic oral bioavailability associated with drugs.

One of the techniques commonly used to overcome the problems of poor bioavailability is the prodrug approach, where the physicochemical properties of the drug are improved by bioreversible chemical alteration (Panchagnula and Thomas, 2000). The most common prodrug strategy involves the incorporation of a polar or ionisable moiety into the parent compound to improve aqueous solubility (Stella et al., 1998). Other approaches such as changing polymorphs and reducing melting points have been used to improve solubility of a drug (Ashford, 2002b).

Besides, formulation approaches have been used to improve oral absorption of poorly soluble drugs. The most useful approach to improve solubility of an insoluble drug in water is to form water-soluble salts. If salt formation is not possible, a series of formulation approaches including pH adjustment, use of water-miscible cosolvents, surface-active agents, complexing agents and liposomes have been investigated (Panchagnula and Thomas, 2000).

Complexing agents such as cyclodextrins are often used to increase the bioavailability of poorly water-soluble or unstable drugs. Complexation of water insoluble drugs usually involves the incorporation of the drug within the inner core of the complexing agent to improve solubility (Jackson et al., 2000). For example, the solubility of miconazole in water was increased upon complexation with cyclodextrins, leading to an increase in its dissolution rate and oral bioavailability (Tenjarla et al., 1998).

Formulation of hydrophobic drugs into solid dispersions has also been employed to improve their dissolution and bioavailability. Solid dispersions consist of a water-soluble carrier and a hydrophobic drug dispersed in the carrier system. The hydrophilic carriers commonly used to formulate solid dispersions include PEG, polyvinyl pyrrolidone (PVP) and hydroxypropylmethyl cellulose (HPMC) (Jackson et al., 2000). PEG has been used to formulate solid dispersions with many types of drugs, including piroxicam

(Fernández et al., 1993), norfloxacin (Guyot et al., 1995) and ibuprofen (Ghosh et al., 1998). In all cases, increases in dissolution and bioavailability of the drug, were observed.

On the other hand, adsorption of drug molecules onto surface of excipients with a small particle size or micronized excipients can reduce drug particle size and increase the surface area of drug available for dissolution. Both of these effects might increase dissolution and, as a result, bioavailability (Jackson et al., 2000). When indomethacin was formulated as an adsorbate with kaolin, an increase in dissolution was observed as compared to a simple mixture of the two components (Alsaidan et al., 1998).

1.2 Adsorption of drugs

1.2.1 Introduction

Excipients are traditionally regarded as inert, and pharmacologically and toxicologically inactive (Pifferi et al., 1999). However, recent findings have shown that drugs and excipients can interact and they can have a tremendous impact on the bioavailability of a drug substance when added into a formulation. Most drug-excipient interactions affect the processes of disintegration and dissolution. These interactions also affect the physiological factors such as the pH of the microenvironment, the stability of a drug substance in the gastrointestinal tract and the permeability of gastrointestinal membranes to the drug (Jackson et al., 2000).

A review of the literature on drug-excipient interactions shows that the mechanism of the interaction is often not clear. However, there are several well-documented mechanisms of drug-excipient interactions such as complexation, solid dispersions, chemical interaction and adsorption (Jackson et al., 2000). Adsorption is a term used to describe the process of accumulation of the atoms, ions, or molecules of a gas or other liquid at the surface of a solid (Marchal-Heussler and Barra, 2002). The adsorption

which has generated most interest is that of a solute in solution on to a solid (Fell, 2002).

Adsorption is essentially a surface effect. Generally, there are two types of adsorption: physical adsorption, in which the adsorbate is bound to the surface through the weak van der Waals forces, and chemical adsorption, which involves the stronger valence forces (Florence and Attwood, 1988b). Physical adsorption usually involves small energy, with adsorption and desorption normally being rapid. Multilayer adsorption is possible, and desorption takes place without chemical change. On the other hand, chemical adsorption is restricted to the formation of a monolayer (Monkhouse and Lach, 1972). However, both physical and chemical adsorptions may be involved in a particular adsorption process. This is the case with the adsorption of toxins in the stomach by attapulgite and kaolin (Florence and Attwood, 1988b).

1.2.2 Adsorption isotherms

The study of adsorption from solution generally involves the determination of an amount of solute adsorbed, x , by a given mass, m , of the adsorbent at constant temperature. Determinations are carried out at different equilibrium concentrations, C , to yield an adsorption isotherm (Fell, 2002).

The isotherms obtained can generally be classified into four characteristic classes, based on the form of the initial part of the isotherm; and each class can be divided into subgroups in relation to the behaviour at higher concentrations. They are shown in Figure 1.1. The L (Langmuir) class is the most common and is characterized by an initial region which is concave to the concentration axis. The L2 isotherm reaches a plateau and further adsorption above this value gives the L3 isotherm, and if that reaches a second plateau it is designated as L4. The fifth L type reflects a special set of circumstances. They are observed with solutes that associate in solution and contain

highly surface-active impurities. For the S (slow) class, the initial slope is convex to the concentration axis, and this is frequently followed by a point of inflection leading to an S-shaped isotherm. The H (high affinity) class results from extremely strong adsorption at very low concentrations giving an apparent intercept on the ordinates while the C (constant partition) class has an initial linear portion which indicates constant partition of the solute between solution and adsorbent and this is observed with microporous adsorbents (Giles et al., 1960, 1974, Martin, 1993, Fell, 2002).

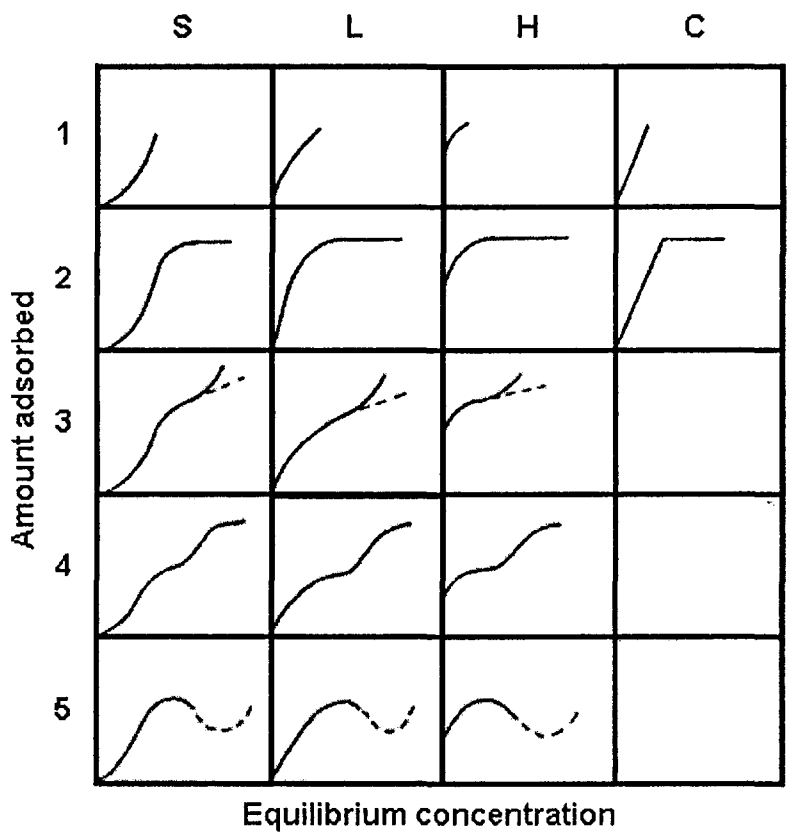


Figure 1.1 Classification of isotherm shapes (adapted from Giles et al., 1960, 1974)

There have been many attempts to develop equations to fit the experimentally observed isotherms. Among the most widely used equations are the Langmuir adsorption isotherm, the Freundlich adsorption isotherm and the Brunauer, Emmett and Teller (BET) equations (Martin, 1993). However, in the current study, only the first two adsorption isotherms are used, and they are discussed in the following sections.

1.2.2(a) Langmuir adsorption isotherm

The equation was derived by assuming that only monolayer coverage was possible.

The equation is usually written as

$$\frac{x}{m} = \frac{abC}{1 + bC} \quad (1.1)$$

where x is the amount of solute adsorbed by a weight, m , of adsorbent. C is the concentration of the solution at equilibrium, and b and a are constants. Equation 1.1 can be arranged into the linear form

$$\frac{C}{(x/m)} = \frac{1}{ab} + \frac{C}{a} \quad (1.2)$$

Hence plotting $C/(x/m)$ against C should give a straight line with a slope $1/a$ and intercept $1/ab$ (Florence and Attwood, 1988b, Martin, 1993, Fell, 2002).

1.2.2(b) Freundlich adsorption isotherm

The Freundlich equation is given as

$$\frac{x}{m} = kC^{1/n} \quad (1.3)$$

where n and k are constants for a particular system. Equation 1.3 can be written in a linear form by taking logarithms of both sides, giving

$$\log \left(\frac{x}{m} \right) = \log k + \left(\frac{1}{n} \right) \log C \quad (1.4)$$

A plot of $\log (x/m)$ against $\log C$ should be linear, with an intercept of $\log k$ and slope of n^{-1} . It is generally assumed that, for systems which obey this equation, adsorption

results in the formation of multilayer rather than a single monolayer (Florence and Attwood, 1988b, Fell, 2002).

1.2.3 Factors affecting adsorption

1.2.3(a) Solubility of the adsorbate

Solubility is an important factor affecting adsorption. According to Lundelius' rule, the extent of adsorption of a solute is inversely proportional to its solubility in the solvent from which adsorption occurs (Florence and Attwood, 1988b). In order for adsorption to occur, solute-solvent bonds must first be broken. Therefore, the greater the solubility, the stronger are these bonds and hence the smaller the extent of adsorption. Besides, it was shown that for most cases of adsorption from solution, the relative amount of solute removed is greater in dilute solutions (Fell, 2002).

1.2.3(b) pH

pH can affect adsorption in various manner, the most important from a pharmaceutical viewpoint being its effect on the ionisation and solubility of the adsorbate drug molecules. Generally, adsorption increases as the ionisation of the drug is suppressed and the extent of adsorption reaching a maximum when the drug is completely unionised (Florence and Attwood, 1988b).

Normally, pH and solubility effects act in concert, since the unionised form of most drugs in aqueous solution has a low solubility. The solubility effect is usually the stronger among the two effects (Florence and Attwood, 1988b). In the adsorption of hyoscine and atropine on magnesium trisilicate, it was observed that hyoscine, although in its completely unionised form, was less strongly adsorbed than atropine, which at the pH of the experiment was 50 per cent ionised. The reason for this result is clear when the solubilities of the two bases are considered. Hyoscine base is freely soluble compared with atropine base. Even when it was 50 per cent ionised, atropine is

less soluble than hyoscine and consequently more strongly adsorbed (El-Masry and Khalil, 1974).

1.2.3(c) Nature of the adsorbent

The physicochemical nature of the adsorbent can have profound effects on the rate and capacity of adsorption. The most important property affecting adsorption is the surface area of the adsorbent. The extent of adsorption is proportional to the specific surface area (Florence and Attwood, 1988b). Thus, an increased surface area, achieved by a reduction in particle size or the use of a porous material, will increase the extent of adsorption (Fell, 2002).

Besides, adsorbent-adsorbate interactions may affect adsorption. These interactions are complex. Some particular adsorbents have affinities for particular adsorbates for a wide variety of reasons. The adsorbent clays such as bentonite, attapulgite and kaolin have cation-exchange sites on the surface. Such clays have strong affinities for protonated compounds which they adsorb by an ion-exchange process. Moreover, different parts of the surface of the same adsorbent may have different affinities for different types of adsorbents (Florence and Attwood, 1988b).

1.2.3(d) Temperature

Adsorption is generally an exothermic process. Therefore, an increase in temperature normally leads to a decrease in the amount adsorbed (Fell, 2002). The changes in enthalpy of adsorption are usually of the order of those for condensation or crystallisation. Thus, small variations in temperature tend not to alter the adsorption process to a significant extent (Florence and Attwood, 1988b).

1.2.4 Medical and pharmaceutical applications of adsorption

1.2.4(a) Improving drug dissolution/bioavailability

The adsorption of drug molecules onto the surface of excipients can reduce drug particle size and increase the surface area of drug available to the dissolution medium. Both of these effects might increase dissolution and, as a result, bioavailability (Jackson et al., 2000). Microcrystalline cellulose, polyvinylpyrrolidone and kaolin serve most often as adsorbents (Marchal-Heussler and Barra, 2002).

The absorption of weak acid dicumarol in dogs was shown to be enhanced by magnesium hydroxide and magnesium oxide as a result of increased dissolution. This was attributed to the formation of a more readily absorbable dicumarol-magnesium chelate or to an increase in pH of the microenvironment caused by the addition of the excipients (Akers et al., 1973). In another study of indomethacin formulated as an adsorbate with kaolin, an increase in dissolution was observed compared with a simple mixture of the two components. The authors suggested that, indomethacin crystallized on the surface of the adsorbent particles during the formation of adsorbate, leading to an increase in the surface area of drug available for dissolution (Alsaidan et al., 1998).

1.2.4(b) Adsorption of noxious substances from the alimentary tract

Adsorption onto finely divided solids has been utilized beneficially for a long time to remove bacterial toxins and for treatment of intoxication by drugs or chemicals (Nada et al., 1989). The commonly used oral antidotes for reducing the effects of poisoning include activated charcoal, magnesium oxide and tannic acid. Several drugs such as chlorpheniramine, propoxyphene hydrochloride, colchicines, diphenylhydantoin and acetylsalicylic acid are adsorbed effectively by activated charcoal. The interactions of drug molecules on the surface of the charcoal particles involved a non-polar, monolayer adsorption (Florence and Attwood, 1988b).

1.2.5 Adsorption problems in drug formulation

Despite the advantages, adsorption may cause problems in formulation. Drugs and preservatives can be adsorbed by containers and undissolved materials in suspension, thereby reducing their effective concentrations (Fell, 2002). For example, the parabens may be adsorbed on to the solid materials present in a suspension, leading to a loss in antimicrobial activity (Allwood, 1982). The adsorption of insulin on to intravenous administration sets has been reported, as has the adsorption of phenylmercuric acetate, used as a preservative in eye drops, on to polyethylene containers (Aspinall et al., 1980).

1.3 Crospovidone

1.3.1 Introduction

Conventional tablets are formulated to release the active compounds within a relatively short interval in order to achieve optimal drug bioavailability. This is normally achieved by incorporating disintegrants to facilitate the break-up of granules and tablets into fine particles upon exposure to fluids in the gastrointestinal tract (Kottke and Rudnic, 2002).

For several decades, starch has been one of the most widely used disintegrants in tablet manufacturing. However, starch has several drawbacks such as reduced effectiveness at high tablet compression forces and large amounts are needed to achieve the desired performance. Hence, alternative high-performance disintegrants, termed as *super disintegrants*, have been introduced into tablet technology. Super disintegrants permit low use levels and facilitate reliable disintegration (I.S.P., 2000a). Insoluble polyvinylpyrrolidone or cross-linked polyvinylpyrrolidone (crospovidone) are classified as super disintegrants.

1.3.2 Physical and chemical properties of crospovidone

Crospovidone is a white, free flowing, high molecular weight, cross-linked polymer synthesized from the monomer vinylpyrrolidone by a popcorn polymerization technique using a catalyst (Kornblum and Stoopak, 1973, Shah and Augsburger, 2001). Crospovidone particles appear to consist of aggregates of smaller particles that are fused together. This aggregation gives crospovidone a spongy, highly porous appearance (Augsburger et al., 2001). The unique structure of crospovidone provides superior adsorptive capacity and exceptional swelling rate (I.S.P., 1999). The chemical structure of crospovidone is shown in Figure 1.2.

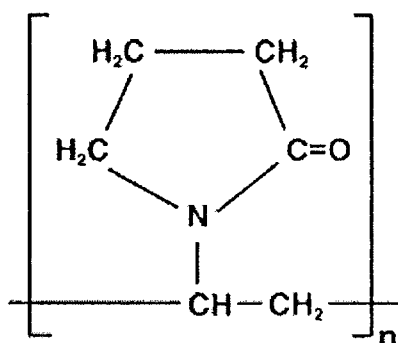


Figure 1.2 Chemical structure of N-vinyl-2-pyrrolidone (I.S.P., 2000a)

Crospovidone is completely insoluble in water and all other organic solvents due to its cross-linked structure. It does, however, swell extremely rapid in water which makes it one of the most widely used super disintegrant for solid dosage forms (I.S.P., 1999). An exact determination of the molecular weight has not been established because of the insolubility of the material (He and Kibbe, 2003). It is chemically inert and no chemical incompatibilities with drug actives have been recorded (I.S.P., 1999).

Particle size distribution of crospovidone and its effect on the flow and swelling properties are important factors to consider for its use in pharmaceutical preparations (Bühler, 1999). Although the coarser grades of crospovidone were found to be more

efficient than those with finer particle sizes in tablet disintegration (Shah and Augsburger, 2001), a grade with relatively fine particle size of around 11 μm was selected for this present study. This is due to the high surface area of the finer crospovidone particles which provide superior adsorptive capacity (I.S.P., 1999).

Crospovidone can form complexes with many molecules including a wide range of drugs as well as toxins. The complexation is reversible, involving the formation of weak hydrogen bonding or van der Waals forces rather than the covalent chemical bonds (I.S.P., 1999). However, complex formation of crospovidone is absent in alkaline medium. Therefore, its ability to reduce the absorption of toxins is controversial and this formed part of the aim of the present study. The degree of complexation also depends on the chemical structure of the drugs used. It has been shown that complexation may increase the rate and extent of drug dissolution (I.S.P., 2000a).

1.3.3 Toxicological and safety profiles

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a non-toxic and non-irritant material. Short-term animal toxicity studies showed that no adverse effect has been associated with crospovidone (He and Kibbe, 2003). The oral median lethal dose (LD_{50}) in rats was more than 100 g/kg. It is not absorbed dermally and not a primary irritant or sensitizer. Long-term clinical studies showed that crospovidone products are not absorbed through the gastrointestinal tract due to its insolubility. It is essentially 100% excreted from the body. The Joint FAO/WHO Expert Committee for food additives has assigned crospovidone an Acceptable Daily Intake status of "Not Specified", since it is not considered a health hazard (I.S.P., 1999, I.S.P., 2000b).